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SHORT COMMUNICATION (PHARMACOMETRICS)

Sample Size Determination for Bioequivalence Assessment Using a Multiplicative Model

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In bioequivalence studies C_{max} and AUC serve as the primary pharmacokinetic characteristics of rate and extent of absorption. Based on pharmacokinetic relationships and on empirical evidence, the distribution of these characteristics corresponds to a multiplicative model, which implies a logarithmic normal distribution in the case of a parametric analysis. Hence, consideration is given to exact and approximate formulas of sample sizes in the case of a multiplicative model.

KEY WORDS: bioequivalence; bioequivalence range; multiplicative model; power; sample size.

In the additive model, i.e., under normality assumption for the untransformed pharmacokinetic characteristics, there is consensus that the assessment of bioequivalence should be based on the $(1-2\alpha)100\%$ confidence interval for the difference of mean bioavailability for test and reference. This procedure is equivalent to the two one-sided tests procedure by means of t tests at nominal level α proposed by Schuirmann (1); consequently, the sample size determination should be based on the power function of this test procedure. Phillips (2) presented exact tables and nomograms using the method of Owen (3) for calculating two definite integrals. Recently, approximate formulas were given by Liu and Chow (4).

Due to the multiplicative effect of clearance, a multiplicative model is postulated for AUC and C_{max}, i.e., a logarithmic normal distribution (5). Taking logarithms of the pharmacokinetic characteristics transforms the multiplicative model on the original scale to the additive model on the

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logarithmic scale; therefore, the latter is also denoted as log-normal linear model (6), and statistical methods developed for the additive model can be used.

Let $\theta = \mu_T/\mu_R$, where μ_T and μ_R denote the median bioavailabilities for test and reference, and let ln denote the natural logarithm. By calculating the exact power for the multiplicative model, Diletti *et al.* (7) showed that in contrast to the (0.8, 1.2) bioequivalence range, the (0.8, 1.25) range results in a power function which has its maximum at $\theta = 1$ (see Fig. 1) and is symmetric about $\ln 1 = 0$ on the logarithmic scale. In other words, for $\theta > 0$ and for the (0.8, 1.25) range, the power at $\ln \theta$ is the same as that at $\ln (1/\theta) = -\ln \theta$ on the logarithmic scale or, equivalently, at θ and $1/\theta$ on the original scale.

These aspects were also reflected in the 1991 U.S. FDA's Generic Drug Advisory Committee (8) vote in favor of the bioequivalence range of 0.8 to 1.25 in the case of the now generally recommended logarithmic transformation of AUC and C_{max} (9,10). Thus, bioequivalence is concluded, if the $(1-2\alpha)100\%$ confidence interval for the ratio of the median bioavailability for test and reference is completely contained in the bioequivalence range (0.8, 1.25).

In analogy to Phillips (2), Diletti *et al.* (7) provided exact sample sizes for the multiplicative model. In the following it is shown that, with minor

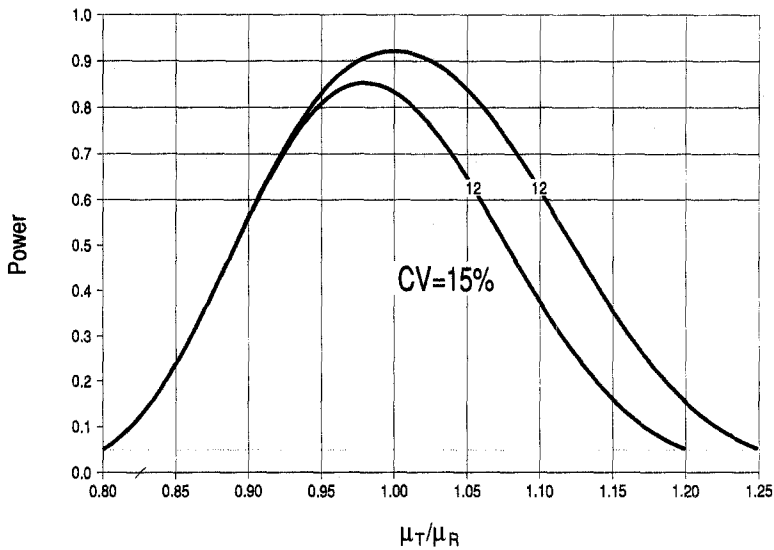

Fig. 1. Probability of correctly concluding bioequivalence (power) in the case of the multiplicative model as a function of the ratios $\theta = \mu_T/\mu_R$ from the interval (0.8, 1.2) and (0.8, 1.25), respectively; power curves refer to sample size of 12 and a CV of 15%.

Table I. Exact (First Line) and Approximate (Second Line) Sample Sizes to Attain a Power of 80 and 90%, Respectively in the Case of the Multiplicative Model[a]

Power (%)	*CV* (%)	$\theta = \mu_T/\mu_R$ 0.85	0.90	0.95	1.00	1.05	1.10	1.15	1.20
80	5.0	12	6	4	4	4	6	8	22
		—	—	—	—	—	—	—	—
	7.5	22	8	6	6	6	8	12	44
		—	—	—	—	—	—	—	—
	10.0	36	12	8	6	8	10	20	76
		—	—	—	—	—	—	—	—
	12.5	54	16	10	8	10	14	30	118
		56	—	—	—	—	—	—	—
	15.0	78	22	12	10	12	20	42	168
		—	—	—	—	—	—	—	170
	17.5	104	30	16	14	16	26	56	226
		106	—	—	—	—	—	58	230
	20.0	134	38	20	16	18	32	72	294
		138	—	—	—	—	—	74	300
	22.5	168	46	24	20	24	40	90	368
		172	48	—	—	—	—	92	378
	25.0	206	56	28	24	28	48	110	452
		212	58	—	—	—	50	114	466
	27.5	248	68	34	28	34	58	132	544
		256	70	—	—	—	60	138	564
	30.0	292	80	40	32	38	68	156	642
		306	82	—	34	40	70	162	670
90	5.0	14	6	4	4	4	6	8	28
		—	—	—	—	—	—	10	—
	7.5	28	10	6	6	6	8	16	60
		—	—	—	—	—	—	—	—
	10.0	48	14	8	8	8	14	26	104
		50	16	—	—	—	—	28	106
	12.5	74	22	12	10	12	18	40	162
		76	—	—	—	—	20	42	164
	15.0	106	30	16	12	16	26	58	232
		108	—	—	—	—	—	—	234
	17.5	142	40	20	16	20	34	76	312
		146	—	—	—	—	—	78	318
	20.0	186	50	26	20	24	44	100	406
		190	52	—	—	26	—	102	414
	22.5	232	64	32	24	30	54	124	510
		238	66	—	—	32	56	128	522
	25.0	284	78	38	28	36	66	152	626
		294	80	—	30	38	68	156	646
	27.5	342	92	44	34	44	78	182	752
		356	96	46	36	46	82	188	780
	30.0	404	108	52	40	52	92	214	888
		422	114	54	42	54	96	224	928

[a] $\alpha = 5\%$; bioequivalence range (0.8, 1.25).

modifications, the approximate formulas of Liu and Chow (4) are also applicable to the multiplicative model.

Let σ^2 denote the residual (within-subject) variance of the logarithmically transformed characteristics, which can be estimated from the mean square error from the corresponding ANOVA, $CV=\sqrt{\exp(\sigma^2)-1}$ the coefficient of variation in the multiplicative model, $t(\alpha, \nu)$ the upper α percentile of the central t distribution with ν degrees of freedom. The total number of subjects required in a two-period crossover design to achieve a $1-\beta$ power at nominal level α is $N=2n$ (n denotes the number of subjects per sequence), where if $\theta=1$

$$n \geq [t(\alpha, 2n-2)+t(\beta/2, 2n-2)]^2[CV/\ln 1.25]^2, \quad (1)$$

if $1<\theta<1.25$

$$n \geq [t(\alpha, 2n-2)+t(\beta, 2n-2)]^2[CV/(\ln 1.25-\ln \theta)]^2 \quad (2)$$

and if $0.8<\theta<1$

$$n \geq [t(\alpha, 2n-2)+t(\beta, 2n-2)]^2[CV/(\ln 0.8-\ln \theta)]^2 \quad (3)$$

Table I gives the total sample sizes to attain a power of at least 80 and 90%, respectively, for $\theta=\mu_T/\mu_R=0.85, \ldots, 1.2$ and various CVs. For the corresponding configuration, the exact sample sizes are given in the first line and the approximate ones in the second line, the latter only if they deviate from the exact ones. As an even number of subjects is needed in a balanced crossover design, calculated odd sample sizes have been rounded up.

Due to the asymmetry of the power curve on the original scale (see Fig. 1), the sample size required, for example, at $\theta=1.1$ is smaller or equal to that at $\theta=0.9$ for the same CV and desired power; however, it is the same at $\theta=0.9$ and $1/\theta=1.111$.

It should be noted, that the sample sizes based on the approximate formulas are generally greater than the exact ones. Notwithstanding this, the proportional differences from the exact values are very small. Therefore, it can be concluded that the approximate formulas (1)–(3) are suitable for the multiplicative model.

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